

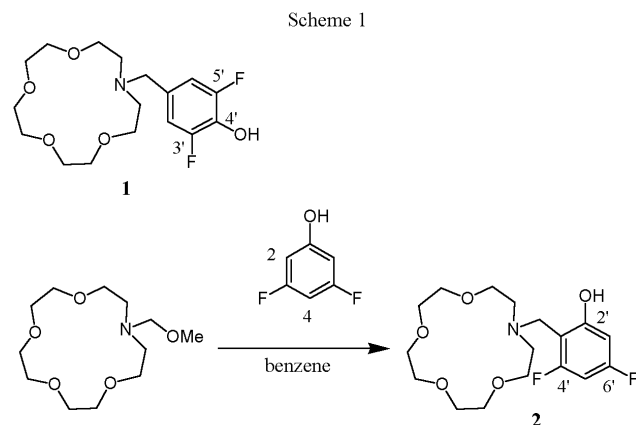
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Armed monoaza-15-crown-5 having a 4',6'-difluoro-2'-hydroxybenzyl group as an additional binding site (**2**) has been prepared by the Mannich reaction of *N*-methoxymethylmonoaza-15-crown-5 with 3,5-difluorophenol. The reactive site on 3,5-difluorophenol for the Mannich reaction was predicted by an electrostatic potential calculation (density functional calculation, SVWN/DN* method). Ligand **2** is interesting, because it has two possible binding sites (phenolic OH group and fluorine atom) in the side arm. An X-ray crystal structure of the potassium thiocyanate complex of ligand **2** revealed that the oxygen atom of the phenolic OH group binds to the potassium cation incorporated in the crown ether ring, and two water molecules are enclosed by two armed crown ethers with the crown ethers forming partition walls.

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A variety of macrocyclic ligands having one or more additional pendant binding sites, so-called armed-crown ethers or lariat crown ethers, has been investigated [1-8]. Recently, we reported that *N*-(3',5'-difluoro-4'-hydroxybenzyl)-monoaza-15-crown-5 (**1**) forms a polymer-like complex with rubidium cations wherein the fluorine atoms of the side arm are involved in complexation [6]. In that complex, the phenolic OH group of the side arm did not participate in forming the polymer-like complex. Those results prompted us to prepare a new armed monoaza-15-crown-5 ether having a phenolic OH group and a fluorine atom at the 2' and 6' positions, respectively, of the side arm (**2**) in order to investigate the possibility of the fluorine atom acting as a binding site. Here we report the synthesis of *N*-(4',6'-difluoro-2'-hydroxybenzyl)-monoaza-15-crown-5 (**2**) and an X-ray crystal structure of its potassium thiocyanate complex. We also report that the calculation of the electrostatic potential is useful to anticipate reactive sites of the reacting phenol in the Mannich reaction and coordination sites in side arms containing more than one donor atom.



3,5-Difluorophenol has two reactive sites for the aminomethylation (see scheme 1). We calculated the electrostatic potential iso-surface [9] by the density functional (SVWN/DN*) method [10] to examine the most reactive site in 3,5-difluorophenol. The electrostatic potential is a function describing the energy of interaction of a point positive charge with the nuclei and the fixed charge distribution of a molecule [11]. The electrostatic potential surface shows the electron-rich region of the molecule. As shown in Figure 1a, the carbon atom at positions 2 (or 6) in 3,5-difluorophenol has the most electron-rich region among the aromatic carbon atoms. Ligand **2** was prepared by the Mannich reaction of methoxymethylmonoaza-15-crown-5 [3] with 3,5-difluorophenol in

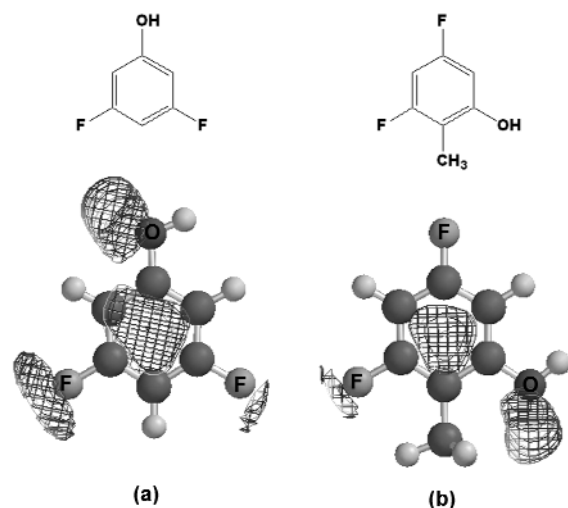


Figure 1. Iso-potential surface of (a) 3,5-difluorophenol (Iso-potential value = -18.5 kcal/mol) and of (b) 3,5-difluoro-2-methylphenol (Iso-potential value = -22.0 kcal/mol) calculated by the density functional calculations (SVWN/DN*) method.

absolute benzene. As expected, the aminomethylation reaction occurred at position 2 as suggested by the electrostatic potential (Figure 1a). The structure of ligand **2** was confirmed by elemental analysis, ^1H nmr and ei-ms methods. Because two aromatic protons were observed as complicated signals at δ 6.4 - 6.3 ppm (Figure 2a), computer ^1H nmr simulation was carried out to analyze the signals [12]. Figure 2b shows the computer-simulated ^1H nmr signals of the aromatic protons of ligand **2**, when coupling constants for $J_{ortho-H-F}$ and $J_{meta-H-H}$ are postulated as 5.5 and 2.8 Hz, respectively. The computer simulation agrees very well with the actual spectrum. The ^1H nmr spectral data clearly suggests that the reaction product is the desired compound **2**. The computer simulation also suggests that a doublet should be observed when aminomethylation occurs at position 4 of 3,5-difluorophenol. Actually, the two aromatic protons of ligand **1** were observed as a doublet [6].

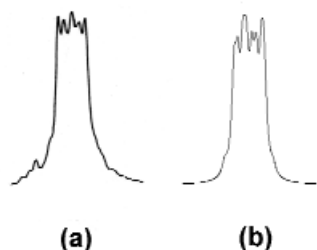


Figure 2. ^1H nmr signals for aromatic protons of **2** (a) and computer-simulated ^1H nmr signals (b).

Ligand **2** has two possible capping sites for metal cations incorporated in the crown ether ring either the OH group at benzyl position 2' or the fluorine atom at position 6'. The structure of the potassium thiocyanate complex with ligand **2** was determined by X-ray crystallography in order to confirm which coordination site has bound to the potassium cation [13]. As shown in Figure 3, the potassium cation

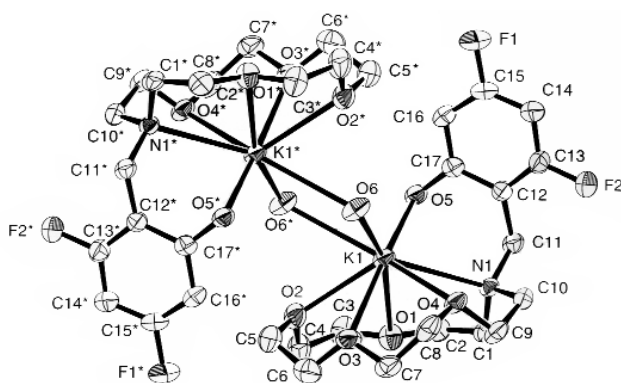


Figure 3. The ORTEP diagram (hydrogen atoms and thiocyanate anion omitted) of **2-KSCN** complex. Selected bond lengths (\AA): K1 - O1, 2.946(6); K1 - O2, 2.827(5); K1 - O3, 2.735(4); K1 - O4, 2.719(4); K1 - O5, 2.867(4); K1 - O6, 2.894(6); K1* - O6, 2.971(5); K1 - N1, 2.992(5); O5 - C17, 1.345(7); F1 - C15, 1.379(7); F2 - C13, 1.347(7).

(K1) was eight-coordinated by the ring nitrogen atom (N1), the ring oxygen atoms (O1, O2, O3 and O4), and the phenolic OH group (O5) of the side arm and water (O6) oxygen atoms. Interestingly, two potassium cations (K1 and K1*) are bridged by two water oxygen atoms (O6 and O6*), whereas the fluorine atoms of the side arm (F1 and F2) and thiocyanate anion do not participate in the coordination. The shortest interatomic $\text{K}^+\text{-N}$ and $\text{K}^+\text{-S}$ distances are 4.37 and 6.61 \AA , respectively. The ligand **2**-potassium thiocyanate system forms a water-bridged 2:2 complex. The two complexes in the system joined by the two water molecules are related by a center of inversion. The dihedral angle between the benzene ring and a plane composed of five heteroatoms (O1, O2, O3, O4, and N1) of the crown ether ring is 103.5° . The two water molecules are enclosed by two ligand **2**'s acting like partition walls. To clarify the structure, Figures 4a and 4b show a Chem-Ray diagram [14] and schematic drawings. Although many crystal structures of alkali metal complexes with crown ether derivatives have been reported, there is no report of a water-bridged potassium complex with 15 membered crown ethers [15]. The present complex is the first such structure.

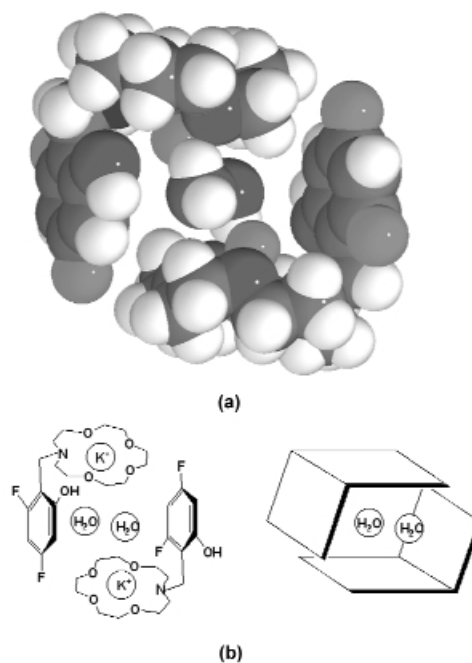


Figure 4. Schematic drawings (a) and the Chem-Ray diagram of **2-KSCN** complex.

We have reported that the electrostatic potential iso-surface is useful to estimate the strongest binding site in an aromatic side arm having dual binding sites [7]. The electrostatic potential iso-surface of 3,5-difluoro-2-methylphenol, a model compound of the side arm portion of ligand **2**, was also calculated. As shown in Figure 1b, the iso-potential surface of the oxygen atom of the

phenolic OH group is larger than that of the fluorine atoms. This result supports the observation that the phenolic oxygen atom preferentially binds a metal cation encapsulated in the crown ether ring rather than a fluorine atom.

Table 1
Crystal and Selected Experimental Data for ligand 2-KSCN

Formula	2-KSCN C ₁₈ H ₂₇ N ₂ O ₆ F ₂ KS
<i>M</i>	476.58
Crystal system	triclinic
Space group	P1- (#2)
<i>a</i> /Å	10.73(1)
<i>b</i> /Å	12.167(10)
<i>c</i> /Å	10.54(1)
α /°	109.06(7)
β /°	110.74(9)
γ /°	96.93(9)
<i>U</i> /Å ³	1171(2)
<i>Z</i>	2
Dc/g cm ⁻³	1.351
<i>F</i> (000)	500.00
μ (Mo-K α)/cm ⁻¹	3.66
Crystal dimensions/mm	0.25x0.20x0.25
No. of reflections for unit cell determination (2 θ range)/°	15 (20.6-23.9)
Scan width/°	1.10+0.30tan θ
Limiting indices	0 ≤ <i>h</i> ≤ 13 -15 ≤ <i>k</i> ≤ 15 -13 ≤ <i>l</i> ≤ 12
No. reflections measured	5663
unique (<i>R</i> _{int})	5377 (0.049)
data used in the refinement	5373
<i>R</i> [all data]	0.193
<i>R</i> _w [all data]	0.217
<i>R</i> 1 [<i>I</i> > 2.0 σ (<i>I</i>)]	0.078
Goodness of fit	1.25
No. parameters, <i>N</i> _p	271
Maximum shift/error in final cycle	0.001
Maximum, minimum peaks in final difference map/e Å ⁻³	0.92, -1.08

*Details in common: ω -2 θ scan; scan range 2 θ 0-55°; $R_w = [\sum w(|F_o| - |F_c|)^2 / \sum w F_o^2]^{1/2}$, $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$, goodness of fit $[\sum w(|F_o| - |F_c|)^2 / (N_o - N_p)]^{1/2}$.

EXPERIMENTAL

The ¹H nmr spectra were measured in deuteriochloroform on a Bruker AC-250 (250 MHz) spectrometer. The ei-ms were performed using the Hitachi M-80 spectrometer.

Preparation of *N*-(4',6'-difluoro-2'-hydroxybenzyl)-1,4,7,10-tetraoxa-13-azacyclo-pentadecane (**2**).

A mixture of *N*-methoxymethylmonoazacrown ether [**3**] (1.0 mmole) and 3,5-difluorophenol (1.0 mmole) in absolute benzene (20 ml) was refluxed under a nitrogen atmosphere for 24 hours. The reaction mixture was cooled and then concentrated under reduced pressure. The residual yellow oil was separated and purified by gel-permeation column chromatography to give ligand **2** in a 20 % yield as an oil; ¹H nmr: δ 6.35 (*J*_{HF} = 5.5 Hz, *J*_{HH} = 2.8 Hz, 1H), 6.35 (*J*_{HF} = 5.5 Hz, *J*_{HH} = 2.8 Hz, 1H), 3.83 (s, 2H), 3.70-3.62 (m, 17H), 2.82 (t, *J* = 5.5 Hz, 4H); ms: ei (m/z) 362 (M⁺ + 1, 100 %).

Table 2
Positional parameters and B(eq) for 2-KSCN

atom	x	y	z	B(eq)
K(1)	0.3260(1)	0.3577(1)	0.7786(2)	3.98(3)
S(1)	0.1866(2)	0.0840(2)	0.9717(2)	6.63(6)
F(1)	0.4492(5)	0.8055(3)	0.6566(5)	7.8(1)
F(2)	0.2398(5)	0.4265(4)	0.2674(5)	7.5(1)
O(1)	0.0509(4)	0.1969(4)	0.6765(5)	5.2(1)
O(2)	0.2410(5)	0.2818(4)	0.9686(5)	5.3(1)
O(3)	0.4233(5)	0.1799(4)	0.8541(5)	5.0(1)
O(4)	0.4077(4)	0.2061(4)	0.5888(5)	4.6(1)
O(5)	0.1530(4)	0.5054(3)	0.6901(4)	4.3(1)
O(6)	0.6227(5)	0.4606(4)	0.9272(5)	6.1(1)
N(1)	0.1346(5)	0.2489(4)	0.4567(5)	3.5(1)
N(2)	0.1959(7)	0.3225(6)	1.0463(7)	6.5(2)
C(1)	0.0143(7)	0.1589(6)	0.4270(7)	4.7(2)
C(2)	0.0432(7)	0.1979(6)	0.5407(8)	5.2(2)
C(3)	0.0121(7)	0.2412(7)	0.7945(8)	6.0(2)
C(4)	0.1036(8)	0.2155(8)	0.9189(8)	6.6(2)
C(5)	0.3418(9)	0.2328(8)	1.0427(8)	6.7(2)
C(6)	0.3719(8)	0.1344(7)	0.9375(9)	6.4(2)
C(7)	0.4474(8)	0.0916(6)	0.7450(8)	5.7(2)
C(8)	0.5014(8)	0.1517(7)	0.6656(8)	5.7(2)
C(9)	0.3015(7)	0.1243(6)	0.4505(7)	5.2(2)
C(10)	0.2161(7)	0.1955(6)	0.3790(7)	4.7(2)
C(11)	0.0868(7)	0.3430(6)	0.4046(7)	4.5(2)
C(12)	0.1941(6)	0.4620(5)	0.4758(7)	3.8(2)
C(13)	0.2585(8)	0.5023(6)	0.4026(8)	5.0(2)
C(14)	0.3491(8)	0.6160(7)	0.4590(8)	5.7(2)
C(15)	0.3646(7)	0.6900(6)	0.5953(9)	4.9(2)
C(16)	0.3032(7)	0.6598(6)	0.6772(7)	4.5(2)
C(17)	0.2169(6)	0.5434(6)	0.6169(7)	3.9(2)
C(18)	-0.1944(7)	0.2216(7)	1.0145(7)	4.6(2)
H(1)	0.2039	0.5949	0.8005	6.3
H(2)	0.0571	0.1394	0.3302	5.9
H(3)	0.0391	0.0860	0.4285	5.9
H(4)	0.0550	0.2798	0.5548	6.3
H(5)	0.1360	0.1478	0.5060	6.3
H(6)	0.0255	0.3284	0.8294	7.2
H(7)	0.0842	0.2068	0.7676	7.2
H(8)	0.0767	0.2312	1.0013	8.0
H(9)	0.0985	0.1274	0.8854	8.0
H(10)	0.3207	0.2072	1.1116	8.0
H(11)	0.4328	0.2973	1.1072	8.0
H(12)	0.2887	0.0689	0.8773	7.4
H(13)	0.4395	0.0975	0.9923	7.4
H(14)	0.5116	0.0515	0.7906	7.2
H(15)	0.3625	0.0295	0.6761	7.2
H(16)	0.5253	0.0932	0.5969	7.0
H(17)	0.5862	0.2124	0.7375	7.0
H(18)	0.3414	0.0777	0.3872	6.8
H(19)	0.2422	0.0653	0.4619	6.8
H(20)	0.2787	0.2592	0.3756	5.9
H(21)	0.1558	0.1447	0.2747	5.9
H(22)	0.0506	0.3129	0.2968	5.5
H(23)	0.0036	0.3552	0.4240	5.5
H(24)	0.3976	0.6418	0.4043	7.3
H(25)	0.3202	0.7182	0.7787	5.9
H(26)	0.7012	0.5369	0.9833	6.3
H(27)	0.6293	0.4263	0.8436	6.3

Anal. Calcd. for $C_{17}H_{25}NO_5F_2$: C, 56.50; H, 6.97. Found: C, 56.72; H, 7.08.

Preparation of Alkali-metal Thiocyanate Complexes with Armed-azacrown Ether, **2**.

Ligand **2** (0.01 mmole) in acetonitrile (1 ml) was reacted with potassium thiocyanate (0.01 mmole). After the solvent had evaporated, the complex was obtained as a pale yellow powder. The powder was dried with an Abderhalden's dryer (50 °C, 0.5 Torr).

Anal. Calcd. for $C_{18}H_{25}N_2O_5SK \cdot CH_3CN$: C, 48.08; H, 5.65. Found: C, 48.14; H, 5.73.

Single crystals for X-ray analysis were obtained by recrystallization from an acetonitrile-water (98/2) solution.

Calculation of Electrostatic Potential Iso-surfaces (Isopotential Surfaces).

The structure was optimized by an *ab-initio* method [11] and then density functional calculations (SVWN/DN*) were used [11]. All calculations were performed using PC Spartan Pro ver.1.05 [16].

Crystallography.

The crystallographic and experimental data are listed in Table 1. The single crystal was mounted in a glass capillary. All measurements were made at 298 K on a Rigaku AFC5S four-circle diffractometer with graphite-monochromated Mo $K\alpha$ radiation (0.71069 Å) and a 12kW rotating-anode generator. Unit cell parameters and the orientation matrix for data collection were obtained using a least-squares procedure. The data were collected using the ω - 2θ scan technique to an above maximum 2θ value of 55.0°. All intensities were corrected for Lorentz and polarization effects. The structure was solved by direct methods (SIR 92) [17]. The non-hydrogen atoms were refined anisotropically. The coordinates of all hydrogen atoms except the hydrogen atoms of the phenolic OH group were calculated at ideal positions (Table 2). Neutral atom scattering factors were taken from Cromer and Waber [18]. Anomalous dispersion effects were included in Fc [19]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuleyl [20]. The values for the mass attenuation coefficients are those of Creagh and Hubbel [21]. All calculations were using the teXsanTM crystallographic software package of Molecular Structure Corporation [22].

Acknowledgement.

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REFERENCES AND NOTES

- [1] Y. Inoue and G. W. Gokel, eds, Cation Binding by Macrocycles, mercel Dekker, Inc, New York, 1990.
- [2] R. M. Izatt, K. Pawlak, J. S. Bradshaw, and R. L. Bruening, *Chem. Rev.*, **91**, 1721 (1991).
- [3] A. V. Bordunov, J. S. Bradshaw, V. N. Pastushok, and R. M. Izatt, *Synlett*, 933 (1996).
- [4] J. S. Bradshaw, A. V. Bordunov, X. X. Zhang, V. N. Pastushok, and R. M. Izatt, *ACS Symp. Ser.*, **716**, 133 (1999).
- [5] Y. Habata, S. Akabori, R. M. Izatt, and J. S. Bradshaw, *Ind. Eng. Chem. Res.* in press.
- [6] Y. Habata, T. Saeki, S. Akabori, X. X. Zhang, and J. S. Bradshaw, *Chem. Comm.*, 1469 (2000).
- [7] Y. Habata, T. Saeki, S. Akabori, X. X. Zhang, and J. S. Bradshaw, *J. Heterocyclic Chem.*, **38**, 253 (2001).
- [8] Y. Habata, T. Saeki, and S. Akabori, *J. Heterocyclic Chem.*, in press.
- [9] W. J. Hehre, J. Yu, P. E. Klunzinger, and L. Lou, A Brief Guide to Molecular Mechanics and Quantum Chemical Calculations, Wavefunction Inc., Irvine, 1998, p 138.
- [10] Reviews of density functional theory: [a] R. O. Jones and O. Gunnarsson *Revs. Mod. Phys.*, **61**, 689 (1989); [b] R. G. Parr and W. Yang, *Density Functional Theory of Atoms and Molecules*, Oxford Univ. Press, Oxford, 1989; [c] J. K. Labanowski and J. W. Andzelm, Eds., *Density Functional Methods in Chemistry*, Springer-Verlag, New York, 1991.
- [11] W. J. Hehre, *Practical strategies for electronic structure calculations*, Wavefunction: Irvine, 1995; p 231.
- [12] g-NMRTM version 4.1.0., released 1995, Ivory Soft, Oxford, OX4 4GA, UK.
- [13] Since the atomic weights of fluorine atoms and oxygen atoms are similar, the structure was solved by changing the O5 atom for the F2 atom to give the following result; R1 = 0.082, R = 0.199, Rw = 0.234, and Goodness of fit = 1.39. When the O5 atom was exchanged for the F1 atom, R1, R, Rw, and Goodness of fit were also 0.082, 0.199, 0.234, and 1.39. Therefore, we confirmed that the structure shown in Figure 3 is correct, because values of R1, R, Rw and Goodness of fit were the lowest (Table 1).
- [14] J. W. Lauher, *J. Mol. Graphics*, **8**, 34 (1990).
- [15] We carried out the document retrieval using ConQuestTM ver. 1.0 (database ver. 5.19, April 2000), the Cambridge Crystallographic Data Center, 2000.
- [16] PC Spartan Pro Ver 1.03, Wavefunction: Irvine, CA, 1999.
- [17] A. Altomare, M. C. Burla, M. Camalli, M. Cascarano, C. Giacovazzo, A. Guagliardi and G. Polidori, *J. Appl. Cryst.*, **27**, 435 (1994).
- [18] D. T. Cromer and J. T. Waber, *International Tables for X-ray Crystallography*, Vol **IV**, The Kynoch Press, Birmingham, England, 1974, Table 2.2A.
- [19] J. A. Ibers and W. C. Hamilton, *Acta Crystallogr.*, **17**, 781 (1964).
- [20] D. C. Creagh and W. J. McAuley, *International Tables for Crystallography*, Vol **C**, (Wilson, A. J. C. Ed.), Kluwer Academic Publishers, Boston, 1992, Table 4.2.6.8, pp 219-222.
- [21] D. C. Creagh and J. H. Hubbell, *International Tables for Crystallography*, Vol **C**, (Wilson, A. J. C. Ed.), Kluwer Academic Publishers, Boston, 1992, Table 4.2.4.3, pp 200-226.
- [22] TeXsanTM: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1999).